A short introduction to morphoelasticity: the mechanics of growing elastic tissues.

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Abstract Growth is a key process in the life and development of all biological organisms and depends on a number of genetic, biochemical, environmental, and mechanical factors. In particular, growth can be affected by mechanical stresses and, in turn, generate new stresses to modify shape, create patterns, and tune the overall response of the tissue. From a mathematical perspective, the modelling of growth processes and in particular its interplay with mechanics is particularly challenging since, unlike traditional mechanical systems, the reference state where key physical quantities need to be evaluated evolve with time. An extra difficulty comes from the fact that the geometry of the object also evolves in time due to the addition of mass. From a modelling perspective, it is particularly important to isolate these effects as they are generated by different processes. In this short introduction, we first give a general overview of the problem of biological growth. Second, the mathematical problem of growth modelling for biological system is considered and illustrated on a number of examples starting with simple one-dimensional systems. Third, we present the general framework of nonlinear morphoelasticity to describe the mechanical response of growing elastic tissues and the remodelling of material properties. The first few introductory pages of these lecture notes are reproduced from (Goriely and Moulton, 2010)

1 Introduction

Growth is the process by which a body increases in size through the addition of mass. In biological systems, growth can serve a number of different purposes, and occurs in many different forms. Growth may be restricted to particular locations on the body. In particular, tip growth is often found in microscopic filamentary systems (Gooday and Trinci, 1980; Howard and Valent, 1996; Goriely and Tabor, 2003). Surface growth and accretion refers to the deposition of material on the surface of a body - this type of growth

is found in the formation of horns, teeth, and seashells (Skalak and Hoger, 1997; Thompson, 1992). In volumetric growth, on the other hand, growth occurs throughout the bulk of the body. This is common in the growth of hearts, tumors, arteries, the brain and airways (Taber and Humphrey, 2001; Cowin, 2004; Budday et al., 2014; Moulton and Goriely, 2011).

Continuum mechanics and nonlinear elasticity provide a natural framework to study growth. Of foremost importance is capturing the correct relationship between growth and elasticity. The basic idea is that in a growth process, the deformation of a body can be due to both a change of mass, and an elastic response. This concept, first put on mathematical terms by Rodriguez et al. Rodriguez et al. (1994), states that the deformation tensor can be decomposed into a growth tensor instructing different parts of the body how to add mass locally and an elastic tensor which captures the elastic reorganization necessary to ensure integrity of the body.

A key benefit to studying growth through continuum mechanics is that it provides direct access to stresses. The relationship between stress and growth is a key concept in the theory of elastic growth. Stress may induce growth, for instance a body may grow until a homeostatic "target" stress is reached. On the other hand, growth can induce residual stress, in particular when the body is inhomogeneous or growing differentially. Residual stresses are stresses that persist in the body even after all body forces have been removed. They are known to play an important role in the functioning of a body. For instance, residual stress is key in the regulation of the transmural stress in arteries (Humphrey, 2003), and is also known to occur in tree and plant tissues (Vandiver and Goriely, 2008), leading to tension or compression woods. A particularly spectacular example of these internal stresses is found in the "Wapas" trees in French Guiana. Due to residual stress, these trees explode when cut, giving them the nickname "killing trees" (Détienne and Thiel, 1988). More generally, the generation of residual stress is connected to the question of how growth can alter the properties of a material (Goriely and Ben Amar, 2005; Ben Amar and Goriely, 2005).

These lecture notes are structured as follows. We begin with a 1D theory of growth, providing several examples to illustrate the basic concepts and some of the questions that arise in morphoelasticity (a complete treatment of one-dimensional growth is presented in (Moulton et al., 2012; Lessines et al., 2014)). Then, we develop the full 3D theory from first principles. In particular we discuss in details issues related with the thermodynamics of growing materials.
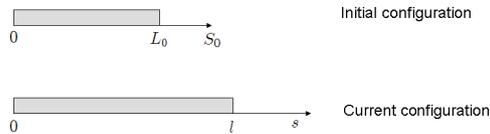
Figure 1. One-dimensional deformation of a rod.

2   1D growth

In this section we develop the theory of elastic growth in one dimension. Consider a rod of length L_0 in its initial reference configuration which undergoes a deformation so that it is of length l in the current configuration. Let S_0 describe position along the rod in the initial configuration and s position in the current configuration - see Figure 1. We define the geometric stretch

$$\lambda = \frac{\partial s}{\partial S_0}. \tag{1}$$

In general $\lambda = \lambda(S_0)$, and λ is constant for a uniform stretch. Also, $\lambda > 1$ corresponds to elongation and $\lambda < 1$ to a reduction. We next consider several classes of deformation.

2.1   Pure elastic deformation

In a pure elastic deformation, $\lambda = \alpha$, where $\alpha = \frac{\partial s}{\partial S}$ is the *elastic stretch*. Letting σ denote the stress, the characteristics of the deformation are determined by a constitutive relationship between σ and α. For example, "Hooke's Law" for a linear material gives $\sigma = E(\alpha - 1)$, where E is the Young's modulus. Solving for α and inserting in (1), the deformation is described by

$$s = \left(\frac{\sigma}{E} + 1\right) S_0, \tag{2}$$

from which we can write $l = \left(\frac{\sigma}{E} + 1\right) L_0$. In this case, the length increases linearly with the stress. A more accurate description is given by the non-linear neo-Hookean relationship $\sigma = \mu(\alpha^2 - \alpha^{-1})$, where $\mu > 0$ is the elastic modulus. This relationship is derived in the contribution by Ogden and Saccomandi in this volume.

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2.2 Pure growth

A pure growth is characterized as having no elastic response. Here, $\lambda = \gamma$, where $\gamma = \frac{\partial S}{\partial S_0}$ describes the growth. Whereas in the previous section α describes a pure elastic *stretch*, γ describes the *addition* or *removal* of material. If $\gamma > 1$ there is growth while $\gamma < 1$ indicates shrinking or resorption of material. In general, the material may undergo growth or resorption at different times and at different rates, and a constitutive relation is needed. For pure growth, the constitutive law is of the form

$$\frac{\partial \gamma}{\partial t} = G(\gamma, s, S_0). \tag{3}$$

In the simple case of uniform growth, $G = 1$, which gives $\gamma = t$ and $s = S_0 t$. Exponential growth is captured by $G = k\gamma$. Then $s = S_0 e^{kt}$ and the length of the rod grows as $l(t) = L_0 e^{kt}$. Alternatively, suppose that growth only occurs towards the tip. For an exponentially growing tip, we take

$$\frac{\partial \gamma}{\partial t} = G(\gamma, s) = \begin{cases} k\gamma & 0 < s < a \\ 0 & a < s < l \end{cases} \tag{4}$$

Equation (4) is coupled with $\frac{\partial s}{\partial S_0} = \gamma$ and initial conditions $s(0) = S_0$ and $\gamma(0) = 1$. The difficulty computationally is that $s = s(S_0, t)$ is a moving interface. To understand the behavior of the growing tip, consider a discrete numeric process. At time t_i, the rod will grow according to $\gamma_i = e^{kt_i}$. How much does the rod grow in one time step, from t_i to t_{i+1}? Letting s_n be the current configuration at the nth step, we have

$$e^{kt_i} = \gamma_i = \frac{\partial s_{i+1}}{\partial S_0} = \frac{\partial s_{i+1}}{\partial s_i} \frac{\partial s_i}{\partial S_0} = \frac{\partial s_{i+1}}{\partial s_i} e^{kt_{i-1}}. \tag{5}$$

This implies that $\frac{\partial s_{i+1}}{\partial s_i} = e^{k(t_i - t_{i-1})} = e^{k\Delta t}$. Thus the region $0 < s_i < a$ grows by a factor $e^{k\Delta t}$, meaning that the rod extends by an amount $\Delta l = a(e^{k\Delta t} - 1)$. The important thing to note is that this is independent of the actual time, *i.e.* the rod extends by the same amount at every time step. Even though the tip is growing exponentially, the length of the rod is only increasing *linearly*.

2.3 Example: the kinematics of tumour growth

As a second example, we present a toy model for tumor growth. Our aim is to write a model of tumour growth for a three dimensional tumour considered as a growing spheroid. Experimentally, cancer cells can be cultured
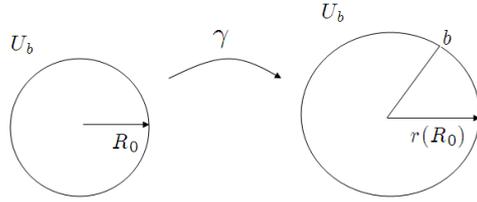
Figure 2. Setup for the tumor growth toy model.

in vitro to grow on a gel or in a pool of nutrients and form a sphere-like shape, the spheroid Sutherland (1988); Freyer et al. (1990). These spheroids are of great interest as they can be used in a variety of settings to understand the response of cancer cells under different physical, chemical, and genetic treatments Santini and Rainaldi (2000); Helmlinger et al. (1997). Mathematically, the spherical symmetry of these aggregates allows for a reduction of the problem difficulty by only considering the evolution of the radius (Franko and Freedman, 1984; Adam and Maggelakis, 1990; Byrne and Chaplain, 1995; Friedman, 2006; Roose et al., 2007).

The setup is depicted in Figure 2. The tumor is surrounded by a bath of nutrient, which is transmitted to the tumor through diffusion with uptake. We first write a one dimensional model. And consider the problem of the growth of a line due to nutrient intake. The centre of tumour is represented by the side of the line at $S_0 = 0$. Nutrient diffuses in from the tip at $S_0 = L_0$. We first assume that the tumour is allowed to growth without being compressed by surrounding healthy tissues. The line concentration of nutrient is labelled $u(s, t)$. The concentration of nutrient in healthy tissues is labelled u_0. Its initial reference length is parameterised by S_0. Any region of the tumour (and in particular the one which is between 0 and S) grows proportionally to its nutrient intake:

$$\partial_t S(S_0, t) = \kappa \int_0^{s(S_0, t)} u(x, t) \mathrm{d}x, \tag{6}$$

where S parameterised the reference arc-length of the tumour and s its current arc length. Taking one partial derivative of (6) by S_0 leads to the local law:

$$\partial_t \gamma = \kappa \, \alpha \, \gamma \, u. \tag{7}$$

The nutrient dynamics is assumed to follow Fick's law of diffusion with a sink term Q accounting for the nutrient consumed by the tumour:

$$u_t = Du_{ss} - Q. \tag{8}$$

We distinguish Phase 1 during which the nutrient fully permeates the tumour from Phase 2 in which the tumour has grown so large that the nutrient no longer reaches its core. As a result, a necrotic core forms and only the periphery of the tumour receives nutrient. We do not model a later phase where vascularisation occurs.

In Phase 1, the boundary conditions are $u(l) = u_0$, and $u_x(0) = 0$ accounting the no-flux condition through the core of the tumour. Assuming that the characteristic time scale for diffusion is much shorter than that of growth, we solve (8) independently of (7) and find

$$u(s,t) = \begin{cases} u_0 & \text{if } s > l, \\ \dfrac{u_l}{a^2}\left(s^2 + a^2 - l^2\right) & \text{if } s \leq l, \end{cases} \tag{9}$$

where l is the position of the front of the tumour and $a = \sqrt{\frac{2Du_0}{Q}}$ is the permeation length of the nutrient.

Substituting (9) in (6) leads to

$$\begin{aligned} \partial_t S &= \frac{\kappa\, u_0}{a^2} \int_0^S \left(x^2 + a^2 - l^2\right) \mathrm{d}x \\ &= \frac{\kappa\, u_0}{a^2} \left(\frac{S^3}{3} + (a^2 - l^2)S\right). \end{aligned} \tag{10}$$

Specialising (10) to the tumour front ($S = l$) gives

$$\partial_t l = \kappa u_0 l \left(1 - \frac{2}{3}\frac{l^2}{a^2}\right). \tag{11}$$

Eq. (11) indicates that growth is exponential in Phase 1.

When $l > a$, the nutrient does not diffuse to the inner most part of the tumour and a necrotic core forms. The point $l = a$ marks the onset of Phase 2. At this point, a new concentration profile occurs defined by the boundary conditions $u(l) = u_0$ and $u(l - a) = 0$. The concentration profile becomes

$$u = \begin{cases} u_0 & \text{if } x > l, \\ \dfrac{u_0}{a^2}\left(x - (l-a)\right)^2 & \text{if } l - a \leq x < l, \\ 0 & \text{if } x < l - a, \end{cases} \tag{12}$$

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where l and a are defined as before and are once again $u(x)$ is C^1 by construction. Also note that the profiles (9) and (12) are identical when $l = a$.

Substituting (12) in (6) and specialising to the tumour edge ($S = l$) leads to

$$\begin{aligned} \partial_t l &= \frac{\kappa\, u_0}{a^2} \int_{l-a}^{l} \left(x - (l-a)\right)^2 \mathrm{d}x \\ &= \frac{\kappa u_0 a}{3}, \end{aligned} \tag{13}$$

which is explicitly solved by

$$l(t) = a + \frac{\kappa\, u_0 a}{3}(t - t_{\mathrm{cr}}), \tag{14}$$

where t_{cr} is the time at which the exponential growth satisfying (11) reaches $l = a$ whence subsequent growth obeys the linear law (14).

Although the simple model (7,8) correctly predicts the apparition of a necrotic core it can easily be improved. We now show how to modify (7,8) to take into account the three-dimensional shape of the tumour. Referring back to the sketch 2, we define $r(R_0, t)$ as the radial position for a solid sphere in the current configuration, where R_0 is the radial position in the initial configuration, and $b(t)$ as the radius in the current configuration. We assume that growth is exponential but proportional to the concentration of the nutrient. Hence, growth is modelled by

$$\begin{aligned} \frac{\partial \gamma}{\partial t} &= k\gamma u(r) \\ \frac{\partial r}{\partial R_0} &= \gamma. \end{aligned} \tag{15}$$

The three dimensional Fick's law reads in spherical coordinates

$$\frac{\partial u}{\partial t} = \frac{D}{r^2} \frac{\partial}{\partial r}\left(r^2 \frac{\partial u}{\partial r}\right) - Q, \tag{16}$$

where D is the diffusion coefficient and Q is the nutrient uptake (assumed to be constant). The outer boundary condition for $u(r,t)$ is $u(b,t) = U_b$, that is the bath provides a constant nutrient supply to the outer surface. The other boundary condition, and the growth behavior, depends on the size of the tumor. If b is small enough so that $u(r)$ can diffuse all the way to the center of the sphere, the boundary condition is $0 \le u(0) < \infty$. For some b_{cr}, the diffusion satisfies $u(0) = 0$. For $b > b_{cr}$, the boundary condition is $u(b - a) = 0$, where $a > 0$ is the penetration length of the nutrient. This is shown schematically in Figure 3.
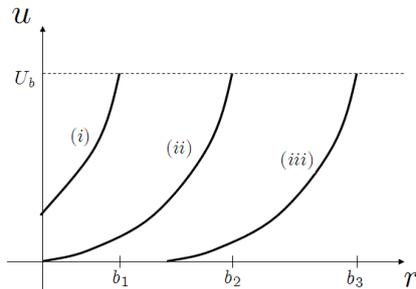
Figure 3. The concentration of the nutrient $u(r)$ as a function of r for different sized tumors. In (i), the tumor radius b_1 is small enough for the nutrient to diffuse all the way to the center, and growth is exponential. In (ii), the radius is a critical value b_{cr} such that $u(0) = 0$. In (iii), $b > b_{cr}$ – here growth only occurs in the region where $u(r) > 0$ and so the growth is linear.

For $b < b_c$, *i.e.* when the tumor is "small", the entire sphere grows and growth is therefore exponential. After this initial phase, growth is restricted to a spherical shell and so is equivalent to the tip growth problem discussed above. Thus, as a function of time, the size of the tumor $b(t)$ increases exponentially at first and then transitions to a linear rate.

Apart from the effect of nutrient, it is believed that mechanical stress has also an effect on growth as high stress may limit the ability of cells to divide through contact inhibition Helmlinger et al. (1997); Hamilton (1998). We will consider this effect in the next Section.

2.4 Growth with elastic response

In an elastic body, growth is subject to an elastic response. The fundamental assumption of morphoelasticity, to be justified later, is that the geometric stretch $\lambda = \frac{\partial s}{\partial S_0}$ is the product of an elastic term α and a growth term γ. That is,

$$\lambda = \alpha\gamma, \tag{17}$$

where α satisfies some constitutive relationship with the stress, $H(\alpha, \sigma) = 0$, and γ satisfies a growth equation $\partial_t \gamma = G(\alpha, \gamma, \sigma)$.

To give an example, consider a rod growing between two walls. We take the growth to be linear and uniform, so that $\gamma = 1 + t$, and use the linear
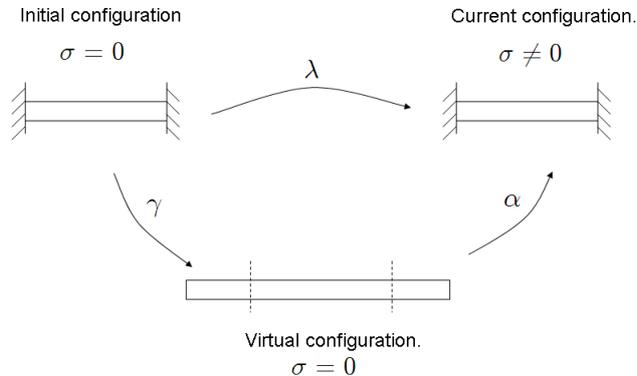
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Figure 4. Decomposition of the deformation into a growth step which leads to an incompatible, virtual configuration, and an elastic response step, which fits the rod back into a physically compatible state and introduces stress.

Hookean model for the elastic relationship: $\sigma = E(\alpha - 1)$. Due to the wall constraint, we must have $\lambda = 1$. This implies $\alpha = 1/\gamma$, from which we obtain

$$\sigma = -E\left(\frac{t}{1+t}\right). \tag{18}$$

Essentially, as the rod grows, a compressive stress builds up to contain the rod in the fixed space. Observe from (18) that as $t \to \infty$, $\sigma \to -E$. This is problematic in that it states that only a finite stress is developed in compressing an infinite rod. The problem is due to the linearity assumption. If instead the non-linear neo-Hookean relationship $\sigma = \mu\left(\alpha^2 + \alpha^{-1}\right)$ is used, we obtain

$$\sigma = \mu\left(\frac{1}{1+t^2} - t + 1\right). \tag{19}$$

For the non-linear model, there is nothing that slows down the growth and $\sigma \to -\infty$ as $t \to \infty$.

To better understand the relationship between growth and elasticity, it is useful to consider a two-step process, pictured in Figure 4. Starting from the initial, stress-free configuration, in Step 1 the rod *grows* to a configuration which is stress free but not compatible because it does not fit within the

walls. Hence this configuration is called a virtual configuration. Step 2 is the elastic response, which may be thought of as the problem of fitting the rod back in between the walls. This step introduces stress, and maps the rod from the virtual configuration to the current configuration.

In many situations, the growth of a body depends on the stress level within the body. For instance, the body may function best at a particular stress, and grow until this target stress is reached. This situation can be modelled by

$$\frac{\partial \gamma}{\partial t} = k\gamma(\sigma - \sigma^*) \tag{20}$$

where σ^* is the target stress or *homeostatic stress*. Consider the rod between two walls geometry and a neo-Hookean material with $\sigma = \mu\left(\alpha^2 - \alpha^{-1}\right)$. As before, $\gamma = 1/\alpha$, and (20) may be recast in terms of α as

$$\frac{\partial \alpha}{\partial t} = \alpha\sigma^* - \mu(\alpha^3 - 1). \tag{21}$$

Setting the right hand side to zero, define α^* as the solution to $\alpha\sigma^* = \mu(\alpha^3 - 1)$, the equilibrium elastic stretch.

Assuming that the initial configuration is stress free, $\alpha(0) = 1$. If $\sigma^* > 0$, $\alpha^* > 1$ and so α will increase up to α^* as $t \to \infty$. This corresponds to γ decreasing from 1 to $\gamma^* = 1/\alpha^*$. In this case, the target stress is tensile, and the rod contracts until the target stress is reached. On the other hand, if $\sigma^* < 0$, the target stress is compressive. Here, $\alpha^* < 1$, and so α decreases to α^*; that is, the rod grows until the proper compression is reached.

2.5 Example: the mechanics of tumour growth

We now revisit the one-dimensional model of tumour growth proposed in Sec. 2.3. In a one dimensional model, we assume that the centre of the tumour is at $s = 0$. In Phase 2 a necrotic core extends until $s = l - a$ followed by growing tissues covering the interval $s \in [l - a, l]$. These two layers compress the healthy tissue trapped between the tumour and the external medium modelled as a fixed wall at distance $d > l$ from the centre of the tumour. The setup is similar to Phase 1 but there are now only two layers since the necrotic core has not yet formed. We allow for necrotic, growing, and healthy tissues to have different mechanical properties. In 1D and in the absence of distributed loads, the stress σ is constant along the length of the structure. We modify the growth law (7) of the active layer to account for the effect of stress on growth:

$$\partial_t \gamma = \kappa\, \alpha\, \gamma\, u \left(1 - \frac{\sigma}{\sigma^\star}\right) H \left(1 - \frac{\sigma}{\sigma^\star}\right), \tag{22}$$

where H is the Heaviside function and $\sigma^\star$ is a critical homeostatic level of stress beyond which growth stops.

The only constitutive assumption needed is that σ is a monotonic function of α. Since necrotic, growing, and healthy tissues may have different constitutive laws, we consider three functions: $\alpha_n(\sigma)$ (in the necrotic tissue), $\alpha_t(\sigma)$ (in the tumour) and $\alpha_h(\sigma)$ (in the healthy tissue).

We restate the problem in dimensionless variables according to

$$t = \frac{t^\star}{\kappa u_0}; \qquad \ell = a\ell^\star; \qquad L_0 = L_0^\star a; \qquad L = aL^\star;$$
$$l = al^\star; \quad \sigma = n\,|\sigma^\star|; \quad u = u_0\,u^\star \tag{23}$$

and drop the *s after rescaling. For instance (22) simplifies to

$$\partial_t \gamma = \alpha\,\gamma\,u\,(1+n)\,H\,(1+n)\,. \tag{24}$$

In Phase 1, the non-dimensionnalised version of (9) is

$$u = \begin{cases} 1 & \text{if } x > l, \\ x^2 + 1 - l^2 & \text{if } x \le l, \end{cases} \tag{25}$$

Note that since the stretches α_t in the tumour and α_h in the healthy tissue are themselves independent of S, we have

$$d = \int_0^L \alpha_t \mathrm{d}S + \int_0^{d-L_0} \alpha_h \mathrm{d}S = \int_0^L \alpha_t \mathrm{d}S + \int_0^{L_h} \alpha_h \mathrm{d}S = L\,\alpha_t(n) + L_h\,\alpha_h(n), \tag{26}$$

which gives an implicit equation for n in function of L. We also have

$$\begin{aligned}
\partial_t L &= \partial_t \int_0^{L_0} \gamma \mathrm{d}S_0, \\
&= H(1+n)\,(1+n) \int_0^{L_0} \alpha\gamma u \mathrm{d}S_0, \\
&= H(1+n)\,(1+n) \int_0^l u \mathrm{d}s, \\
&= H(1+n)\,(1+n) \int_0^{\alpha_t L} s^2 + 1 - (\alpha_t L)^2 \mathrm{d}s, \\
&= H(1+n)\,(1+n)\,\alpha_t L\left(1 - \frac{2}{3}\alpha_t^2\,L^2\right). \tag{27}
\end{aligned}$$

Eqs. (26, 27) together with the constitutive laws for both healthy and tumour tissues form a closed system.
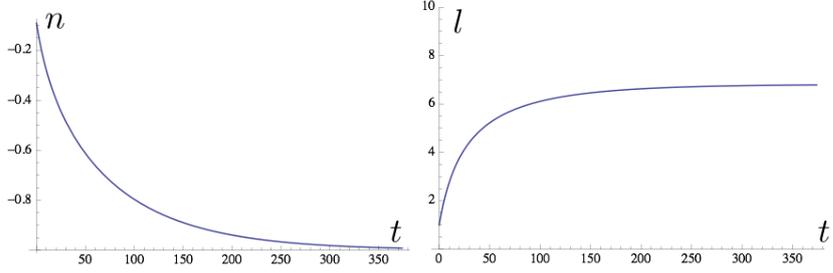
Figure 5. Stress $n[||\sigma^\star||]$ (left) and position of the front $l[a]$ (right) in function of time. For a tumour growing towards an homeostatic stress $\sigma^\star < 0$ when all three tissues are assumed to be Neo-Hookean: $\sigma = \mu_i/3(\alpha_i^2 - 1/\alpha_i)$ where i takes value in $\{n, t, h\}$ and we assumed as an example that $\mu_n = \mu_h = \mu_t = -\sigma^\star$.

In Phase 2 the non-dimensional nutrient profile is

$$
u = \begin{cases} 1 & \text{if } x > l, \\ \left(x + 1 - l\right)^2 & \text{if } l - 1 \le x < l, \\ 0 & \text{if } x < l - 1, \end{cases}
\tag{28}
$$

so that

$$
\begin{aligned}
\partial_t(L_n + L) &= H(1+n)(1+n)\int_0^l u\,\mathrm{d}s, \\
&= H(1+n)(1+n)\int_{\alpha_n L_n}^{\alpha_n L_n + 1}(s - \alpha_n L_n)^2\,\mathrm{d}s, \\
&= H(1+n)\frac{1+n}{3}.
\end{aligned}
\tag{29}
$$

Eq. (26) becomes

$$
d = L_n \alpha_n + 1 + \alpha_h L_h,
\tag{30}
$$

since the growing tissue extends over a current length of

$$
\alpha_t L_t = 1.
\tag{31}
$$

Eqs. (29-31) together with the constitutive laws for each subregions constitute a closed system of equations. The initial value for the differential

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equation (29) is $L_n(0) = 0$. A numerical solution of this system is given in Fig. 5.

For large times, the stress asymptotically reaches the (dimensional) value $\sigma^\star$. Accordingly, the healthy tissue is asymptotically stretched to $\alpha_h(\sigma^\star)$ and the front of the tumour reaches

$$l \overset{t\to\infty}{\to} d - \alpha_h(\sigma^\star)L_h. \tag{32}$$

We conclude that before vascularisation, the final size of the tumour is dictated by the available space d, the constitutive law of *the healthy tissue*, and the homeostatic stress.

3 3D growth

To appropriately model the 3D growth of soft biological tissues aspects of growth and elasticity should be incorporated into a theoretical framework. In their seminal paper, Rodriguez *et al.* (Rodriguez et al., 1994) proposed a multiplicative decomposition of the deformation gradient into growth and elastic parts.

Their work was based on similar ideas from plasticity: The Kröner-Lee decomposition (Kröner, 1960; Lee, 1969) which splits the deformation gradient into an elastic and a plastic part. In this Section, we formally introduce the theory of morphoelasticity, which is an formalisation of Rodriguez *et al.*'s idea. This introduction, much like a traditional derivation of basic equations of nonlinear solid mechanics, will include a part on kinematics (geometric deformation, *i.e.* the study of strains, see Section 3.1), balance laws (balance of forces and other physical quantities, see Section 3.2) and constitutive relationships (which relate strains to stresses, see Section 3.3).

A challenging aspect of morphoelasticity is that (as opposed to traditional nonlinear solid mechanics) morphoelastic systems can be open to fluxes of mass, energy, momentum, and entropy. These quantities must be accounted for carefully. This will be the subject of Section 3.2. It will result in a continuum formulation of the second law of thermodynamics known as the Clausius-Duhem inequality. This formalism will be used Section 3.5 to derive general statements about growth laws.

3.1 Kinematics

In traditional continuum mechanics it is common to consider the body in two different configurations, the *initial reference configuration* and the *current configuration*. The initial reference configuration describes the body in its initial state at $t = 0$ (*i.e.* before deformation) and is required to be
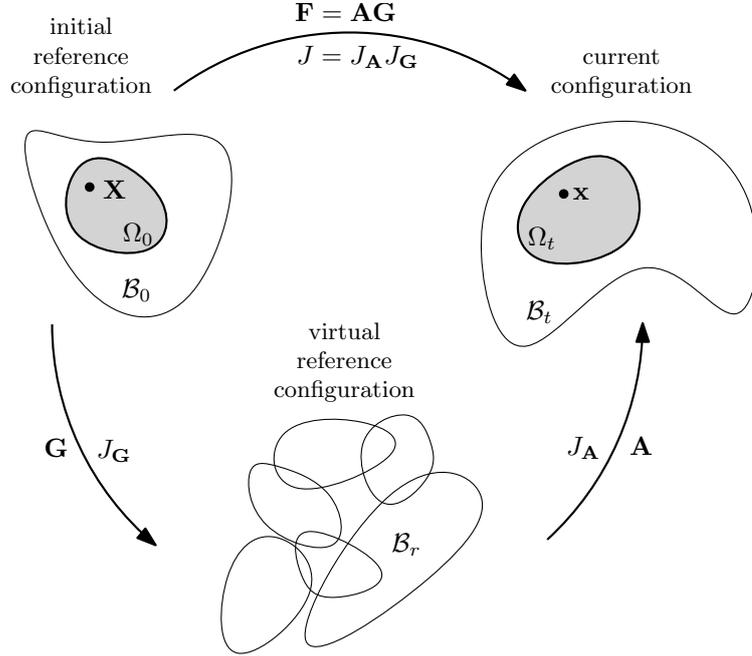
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Figure 6. Deformation gradient decomposition. The fact that the virtual reference configuration $\mathcal{B}_r$ does not fit into Euclidean space is highlighted.

stress-free. The current configuration describes the deformed body at time t. Mathematically, they are subsets of the Euclidean space, denoted $\mathcal{B}_0 \in \mathbb{E}^3$ and $\mathcal{B}_t \in \mathbb{E}^3$, respectively. Material points in $\mathcal{B}_0$ are described by the the vector $\mathbf{X}$ which are mapped to $\mathbf{x}$ in $\mathcal{B}_t$. This deformation map is

$$\boldsymbol{\varphi}: \ \mathcal{B}_0 \to \mathcal{B}_t \qquad \mathbf{X} \mapsto \mathbf{x} = \boldsymbol{\varphi}\left(\mathbf{X}, t\right), \tag{33}$$

for which we assume the inverse $\boldsymbol{\varphi}^{-1}$ to exist. Strain, the geometric deformation of a body $\mathcal{B}_t$ with respect to its reference state in $\mathcal{B}_0$, is quantified through the deformation gradient $\mathbf{F}$. The latter is defined as the gradient of the deformation map with respect to initial reference coordinates

$$\mathbf{F}\left(\mathbf{X}, t\right) = \nabla_{\mathbf{X}} \boldsymbol{\varphi}\left(\mathbf{X}, t\right) = \frac{\partial \mathbf{x}}{\partial \mathbf{X}}\left(\mathbf{X}, t\right). \tag{34}$$

As mentioned in the introduction, in morphoelasticity we decompose the deformation gradient into a growth deformation gradient $\mathbf{G}$ and an elastic

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deformation gradient $\mathbf{A}$:

$$\mathbf{F}(\mathbf{X}, t) = \mathbf{A}\mathbf{G}. \tag{35}$$

This decomposition requires the introduction of the virtual reference configuration $\mathcal{B}_r \in \mathbb{E}^3$. We define the determinants of the deformation gradients as $J := \det \mathbf{F}$, $J_A := \det \mathbf{A}$ and $J_G := \det \mathbf{G}$ and we have $J = J_A J_G$. If the deformation is isochoric (*i.e.* locally volume preserving), $J_A = 1$.

Formally[1], $\mathbf{G}$ maps vectors from $\mathcal{B}_0$ to $\mathcal{B}_r$ and $\mathbf{A}$ maps from $\mathcal{B}_r$ to $\mathcal{B}_t$ and their composition $\mathbf{F} = \mathbf{A}\mathbf{G}$ maps vectors from $\mathcal{B}_0$ to $\mathcal{B}_t$. On a physical level, the decomposition can be interpreted as follows. Growth (geometrically speaking) is a map from a stress-free configuration $\mathcal{B}_0$ to another stress-free configuration $\mathcal{B}_r$, but the latter will in general not fit into Euclidean space as the grown material will overlap or (if locally $\det \mathbf{G} < 1$, *i.e.* resorption) have holes. That is, $\mathbf{G}$ can break the continuity of the tissue. The purpose of the elastic deformation is to restore continuity of the tissue, filling the holes at the expense of introducing tensile stress, and moving apart the overlapping regions at the expense of introducing compressive stress. For this reason, the current configuration $\mathcal{B}_t$ is no longer stress free, even when it is unloaded. Stress that remains even in the absence of loads is called r*esidual stress*.

The configuration $\mathcal{B}_r$ is not physically realised in a growing biological tissue, and for this reason we refer to it as the *virtual reference configuration*. Because of possible overlaps of tissue, a bijective deformation map of the kind (33) cannot be defined between $\mathcal{B}_0$ and $\mathcal{B}_r$ (*i.e.* it is impossible to keep track of material points if $\mathcal{B}_r$ is not Euclidean) and $\mathbf{G}$ cannot be defined as a gradient of a deformation map in the fashion of (34).

3.2 Balance laws

In this section we state the balance laws for mass, linear momentum, angular momentum, energy and the entropy imbalance. The energy balance and the entropy imbalance are continuum formulations of the first and second law of thermodynamics, which leads to the Clausius-Duhem formulation of the second law.

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[1]In the main text, we follow a standard introduction of kinematics in morphoelasticity in which $\mathcal{B}_0$, $\mathcal{B}_r$ and $\mathcal{B}_t$ are Euclidean, which leads to restrictions like the lack of a bijective map between $\mathcal{B}_0$ and $\mathcal{B}_r$.

From a differential geometric perspective, $\mathcal{B}_0$, $\mathcal{B}_r$ and $\mathcal{B}_t$ are differentiable manifolds and $\mathbf{F}$, $\mathbf{A}$ and $\mathbf{G}$ are maps from tangent bundles to tangent bundles of the respective manifolds. From this perspective, $\mathcal{B}_r$ is perfectly compatible at the expense of being non-Euclidean. We will not go further into differential geometric aspects here. Detailed treatments can be found in (Marsden and Hughes, 1994) and (Yavari, 2010).

Generalising the conservation equations of traditional continuum mechanics to morphoelasticity and open systems requires careful balance and the correct interpretation of source terms. These equations have been studied by several authors and we will keep our notation relatively close to Epstein (Epstein, 2012).

Note that the overdot denotes derivatives with respect to the time variable. For some quantity a, we denote the time derivative $\dot{a} = \mathrm{d}a/\mathrm{d}t$. Also note that spatial differentiation (divergence, gradient) is always implied with respect to the current variable $\mathbf{x} \in \mathcal{B}_t$ (unless stated otherwise, like in 34).

Slow growth assumptions of morphoelasticity Having stated the kinematic assumptions of morphoelasticity in the previous section, we now introduce some mechanical assumptions.

1. Separation of timescales: The timescale of growth is much slower than that of elasticity.

2. Mass is added from the initial reference configuration $\mathcal{B}_0$ to the virtual reference configuration $\mathcal{B}_r$ and is constant throughout the elastic deformation (which maps from $\mathcal{B}_r$ to $\mathcal{B}_t$).

3. Mass is added through a volumetric source (*i.e.* no mass boundary flux).

The first assumption is typically valid for biological growth with time scale of the order of hours, days, or years, whereas the timescale of elasticity relates to wave propagation in elastic materials which is no larger than seconds.

We will now briefly explore a consequence of the second assumption and explore the third assumption when stating the mass balance.

We assume that mass is added in the growth process from $\mathcal{B}_0$ to $\mathcal{B}_r$, but no mass is added during the elastic deformation from $\mathcal{B}_r$ to $\mathcal{B}_t$. We define $\mathrm{d}M_r = \rho_r \mathrm{d}V_r$ as the mass element in the virtual reference configuration $\mathcal{B}_r$, where ρ_r is the virtual reference mass density and $\mathrm{d}V_r$ is a virtual reference volume element. Similarly, let $\mathrm{d}M_t = \rho \mathrm{d}V_t$ where ρ is the current density. Since no mass is added from $\mathcal{B}_r$ to $\mathcal{B}_t$, $\mathrm{d}M_t = \mathrm{d}M_r$, and with appropriate volume element transformation $\mathrm{d}V_t = J_A \mathrm{d}V_r$ we obtain

$$J_A \, \rho = \rho_r. \tag{36}$$

We now make the additional assumption that ρ_r is constant in time. This assumption implies that the grown mass has the same density (locally) as the surrounding pregrown tissue. This assumption allows for a simple coupling between the mechanics and geometry of growth.

Mass balance   We think of a growing tissue as a collection of cells which take nutrients from the extracellular fluid. In our continuum modeling approach, the tissue has a density (mass per volume) $\rho(\mathbf{x}, t)$ in $\mathcal{B}_t$. Nutrient uptake contributes a volumetric growth rate function $\rho(\mathbf{x}, t)\gamma(\mathbf{x}, t)$ in $\mathcal{B}_t$. Physical laws are most naturally stated in the current configuration. We will present the mass balance for a volume $\Omega_t \subset \mathcal{B}_t$ on which the mass balance takes the form

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_{\Omega_t}\rho\,\mathrm{d}V_t = \int_{\Omega_t}\rho\gamma\,\mathrm{d}V_t. \tag{37}$$

We now transform this balance equation which is integrated over Ω_t into a local, pointwise statement at $\mathbf{x}$, t. Since Ω_t is a region which evolves with time, it will prove useful to transform to the corresponding region $\Omega_0 \subset \mathcal{B}_0$ and evaluate time derivatives in this static region. Volume elements and area elements transform as

$$\int_{\Omega_t}\mathrm{d}V_t = \int_{\Omega_0}J\,\mathrm{d}V_0. \tag{38}$$

Evaluating time derivatives in $\mathcal{B}_0$ and taking into account that $J_A\,\rho$ is constant in time leads us to the local, pointwise statement

$$\gamma = \mathrm{tr}\left(\dot{\mathbf{G}}\mathbf{G}^{-1}\right). \tag{39}$$

Tht is, for constant mass density, the change in mass of a body to properties of the geometric deformation gradient.

Compatible and incompatible sources   As we have discussed regarding the slow growth assumption, new mass (with the same density as the surrounding material) enters the tissue with the local growth rate $\rho\gamma$. This material will come with its own momentum, energy and entropy. One possibility is that the new material has the same properties as (locally) the surrounding tissue. We call these type of sources *compliant*, using the terminology of (Epstein, 2012), and they balance out and do not appear in the local statements of the laws. Alternatively, the new material may have sources that are different from the pregrown material, having for instance locally a higher energy density than the surrounding tissue, or due to microscopic organisation possibly a lower entropy. We call these sources *non-compliant* (denoted with an overbar), and they do appear in the local statements.

Linear momentum balance The linear momentum balance is the balance between rate of change of linear momentum and the sum of the forces. We introduce the volumetric body force density (force per unit current volume) $\mathbf{b}$, the surface traction (force per area) $\mathbf{t}$ which according to Cauchy's postulate can be decomposed into the Cauchy stress $\mathbf{T}$ times the surface normal $\mathbf{n}$, *i.e.* $\mathbf{t} = \mathbf{Tn}$. The non-compliant momentum source (force per volume) is $\bar{\mathbf{p}}$:

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega_t} \rho\mathbf{v}dV_t = \underbrace{\int_{\Omega_t} \mathbf{b}\mathrm{d}V_t + \int_{\partial\Omega_t} \mathbf{Tn}\mathrm{d}A_t}_{\text{body and traction forces}} + \underbrace{\int_{\Omega_t} \gamma\rho\mathbf{v}\mathrm{d}V_t}_{\text{compliant}} + \underbrace{\int_{\Omega_t} \bar{\mathbf{p}}\mathrm{d}V_t}_{\text{non-compliant}} . \quad (40)$$

After a standard transport and localisation procedure, the local (pointwise) equivalent statement is

$$\rho\dot{\mathbf{v}} = \mathbf{b} + \nabla \cdot \mathbf{T} + \bar{\mathbf{p}}. \quad (41)$$

Angular momentum balance The angular momentum balance is the balance between change in angular momentum and the moments (sometimes also called torques) that balance it. Without loss of generality, we state moments with respect to the coordinate system origin. Since the non-compliant linear momentum source $\bar{\mathbf{p}}$ enters the angular momentum balance, we require no additional non-compliant angular momentum source (it could be include into $\bar{\mathbf{p}}$) and we assume that there is no source of body couple (that is the system is non-polar). We have

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega_t} \rho\mathbf{x} \times \mathbf{v}\mathrm{d}V_t = \underbrace{\int_{\Omega_t} \mathbf{x} \times \mathbf{b}\mathrm{d}V_t + \int_{\partial\Omega_t} \mathbf{x} \times \mathbf{Tn}\mathrm{d}A_t}_{\text{moments through body and traction forces}}$$
$$+ \underbrace{\int_{\Omega_t} \gamma\rho\mathbf{x} \times \mathbf{v}\mathrm{d}V_t}_{\text{compliant}} + \underbrace{\int_{\Omega_t} \mathbf{x} \times \bar{\mathbf{p}}\mathrm{d}V_t}_{\text{non-compliant}} . \quad (42)$$

Localising the angular momentum balance, leads to the symmetry of the Cauchy stress tensor $\mathbf{T} = \mathbf{T}^T$.

Energy balance (first law of thermodynamics) The total energy is made up of internal energy $\mathcal{E}$ (*i.e.* elastic and chemical energy) and kinetic energy $\mathcal{K}$. The mechanical power $\mathcal{P}$ is the work per time which the body is exposed to through body force forces $\mathbf{b}$ and surface traction $\mathbf{t}$, introduced in the context of linear momentum balance. The heating $\mathcal{Q}$ is composed of

a volumetric heat source r (for radiation) and a surface flux $\mathbf{q}$ called the Fourier heat flux. Apart from $\overline{\mathbf{p}}$, the non-compliant energy source $\overline{\varepsilon}$ enters the balance equation:

$$\underbrace{\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega_t} \rho \left(\varepsilon + \frac{1}{2} |\mathbf{v}|^2 \right) \mathrm{d}V_t}_{\dot{\overline{\mathcal{E}(\Omega_t) + \mathcal{K}(\Omega_t)}}} = \underbrace{\int_{\Omega_t} \mathbf{b} \cdot \mathbf{v} \mathrm{d}V_t + \int_{\partial\Omega_t} \mathbf{n} \cdot \mathbf{T}\mathbf{v} \mathrm{d}A_t}_{\mathcal{P}(\Omega_t)}$$

$$+ \underbrace{\int_{\Omega_t} \rho r \, \mathrm{d}V_t + \int_{\partial\Omega_t} \mathbf{q} \cdot \mathbf{n} \mathrm{d}A_t}_{\mathcal{Q}(\Omega_t)}$$

$$+ \underbrace{\int_{\Omega_t} \gamma\rho \left(\varepsilon + \frac{1}{2} |\mathbf{v}|^2 \right) \mathrm{d}V_t}_{\text{compliant}}$$

$$+ \underbrace{\int_{\Omega_t} \overline{\varepsilon} + \overline{\mathbf{p}} \cdot \mathbf{v} \mathrm{d}V_t}_{\text{non-compliant}} . \tag{43}$$

The local (pointwise) statement is

$$\rho\dot{\varepsilon} = \mathbf{T} : \dot{\mathbf{F}}\mathbf{F}^{-1} + \rho r - \nabla \cdot \mathbf{q} + \overline{\varepsilon}. \tag{44}$$

Note that in this derivation, the term $\mathbf{b} \cdot \mathbf{v}$ is be replaced through the linear momentum balance according to (41), which explains why $\overline{\mathbf{p}}$ does not appear in the local statement.

Entropy / free energy imbalances (second law of thermodynamics)
According to the entropy imbalance, the change in entropy density η is greater than the heat supply (as defined in the energy balance) divided by the temperature density θ. The non-compliant energy source $\overline{\varepsilon}$ and the entropy source $\overline{\eta}$ also enter the imbalance.

$$\frac{\mathrm{d}}{\mathrm{d}t} \int_{\Omega_t} \rho\eta \mathrm{d}V_t \geq \underbrace{\int_{\Omega_t} \frac{\rho r}{\theta} \mathrm{d}V_t - \int_{\partial\Omega_t} \frac{\mathbf{q} \cdot \mathbf{n}}{\theta} \mathrm{d}A_t}_{\mathcal{Q}(\Omega_t)/\Theta(\Omega_t)} + \underbrace{\int_{\Omega_t} \gamma\rho\eta \mathrm{d}V_t}_{\text{compliant}} + \underbrace{\int_{\Omega_t} \frac{\overline{\varepsilon} - \overline{\eta}}{\theta} \mathrm{d}V_t}_{\text{non-compliant}},$$

$$\tag{45}$$

which locally takes the form

$$\rho\dot{\eta} \geq \frac{\rho r}{\theta} - \nabla \cdot \left(\frac{\mathbf{q}}{\theta} \right) + \frac{\overline{\varepsilon} - \overline{\eta}}{\theta}. \tag{46}$$

For our analysis of constitutive relationships, it is useful to apply a Legendre transform to the free energy density $\psi = \varepsilon - \theta\eta$. After applying the time derivative and substituting (44) for the internal energy, we obtain the free energy imbalance

$$\rho\dot{\psi} \leq \mathbf{T} : \dot{\mathbf{F}}\mathbf{F}^{-1} - \rho\dot{\theta}\eta - \frac{\mathbf{q} \cdot \nabla_{\mathbf{x}}\theta}{\theta} + \overline{\eta}. \tag{47}$$

This formulation of the second law of thermodynamics in terms of the free energy density is known as the Clausius-Duhem inequality.

3.3 Constitutive relationships

In the context of nonlinear elasticity, a constitutive law or constitutive relationship relates strains to stresses.[2]. For a hyperelastic material, stresses can be derived from a scalar field called the strain-energy function W. Its independent variables depend on the modeling assumptions at hand. Typical assumptions in the context of modelling biological tissues are:
1. Hyperelastic and isothermal materials, *i.e.* strain energy density depends only on the elastic deformation gradient, $W = W(\mathbf{A})$.
2. Incompressible materials, *i.e.* $\det(\mathbf{A}) = 1$.

For incompressible, isothermal, hyperelastic materials the Cauchy stress $\mathbf{T}$ can be derived from the strain energy density as

$$\mathbf{T}(\mathbf{A}) = \frac{\partial W}{\partial \mathbf{A}}\mathbf{A}^T - p\mathbf{1}, \tag{48}$$

where p is a Lagrange multiplier which enforces incompressibility. Incompressibility is a typical assumption for soft biological tissues.

There is generally very little information on constitutive relationships in soft biological tissues (Taber, 1995), and neo-Hookean materials have proven very useful as modeling starting points. The strain-energy density function of a neo-Hookean solid in three dimensions is $W(\mathbf{A}) = \mu(I_1 - 3)$ where μ is a material parameter and I_1 is the first principal invariant of the right Cauchy-Green strain tensor $\mathbf{C} = \mathbf{A}^T\mathbf{A}$ for which $I_1 = \operatorname{tr}\mathbf{C} = \alpha_1^2 + \alpha_2^2 + \alpha_3^2$ where α_i, $i = 1, 2, 3$ are the three principal elastic stretches. We obtain

$$W(\alpha_1, \alpha_2, \alpha_3) = \mu\left(\alpha_1^2 + \alpha_2^2 + \alpha_3^2 - 3\right). \tag{49}$$

3.4 Growth laws and literature review

In morphoelasticity, the evolution of growth is described as a differential equation in time

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[2]Note that in the context of rational thermodynamics, the notion of constitutive relationships carries a wider meaning. This will be discussed in Section 3.5

$$\dot{\mathbf{G}} = \mathcal{G}\left(\mathbf{T}, \mathbf{F}, \mathbf{G}, \boldsymbol{\mu}; t, \mathbf{x}, \mathbf{X}\right),$$

where the dot denotes time differentiation. Here, $\mathbf{F}$ and $\mathbf{G}$ are deformation gradients as described above, $\mathbf{T}$ is the Cauchy stress, $\boldsymbol{\mu}$ can be biochemical or other fields and $\mathbf{x}$ and $\mathbf{X}$ describe positions in the undeformed and deformed body, respectively. The growth law $\dot{\mathbf{G}} = \mathcal{G}$ describes an active growth process which requires energy and adds material, whereas the elastic accommodation (geometrically described by $\mathbf{A}$) is passive, adds no mass and consumes no energy (unless plasticity is involved). The difficulty in stating growth laws is that the observed evolving form and mass of the body are a result of both growth and its elastic accommodation. There is a lack of data for constitutive relationships of biological tissues, let alone successfully retrieved growth deformations $\mathbf{G}$, which makes the growth law $\dot{\mathbf{G}}$ particularly difficult to access.

The study of growth laws is in its infancy. Even the question of whether stress or strain drives growth is not settled, every major review contains a debate on this topic((Taber, 1995; Ambrosi et al., 2011; Jones and Chapman, 2012). Here we take the view that growth laws should be functions of stress $\dot{\mathbf{G}} = \mathcal{G}\left(\mathbf{T}\right)$ as a stress-free configuration can be chosen as reference (a reference configuration for strain is less obvious).

The simplest stress-dependent growth law which incorporates the idea of homeostasis is a linear coupling with Cauchy stress

$$\dot{\mathbf{G}} = \mathbf{G}\mathbf{K}\left(\mathbf{T} - \mathbf{T}^*\right), \tag{50}$$

where $\mathbf{K}$ is a matrix of constant coefficients and $\mathbf{T}^*$ is the homeostatic stress. This was studied in (Ramasubramanian and Taber, 2008). The authors run finite element simulations on variations of two-dimensional beams glued in parallel, finding that (depending on choices of $\mathbf{K}$ and $\mathbf{T}^*$) the system may or may not equilibrate. They also study a delay differential equation version of (50) by replacing $\mathbf{T}\left(\mathbf{x}, t\right)$ with $\mathbf{T}\left(\mathbf{x}, t - \tau\right)$ where τ is a small delay, finding that depending on the delay and the stiffness ratio of beams glued in parallel, either no oscillations, stress oscillations or both stress and curvature oscillations of the beams occur. Finally, the authors study invagination of cylindrical and spherical, fluild-filled or empty shells. Again, they use a finite-element simulation in which the shell consists of passive material with a small striped active region in the shell driving the invagination. They reproduce shapes which somewhat resemble invagination. Overall, their analysis shows that (50) either leads to stationary states of the growing system, or to unrealistic ever-growing systems, depending on the choice of $\mathbf{K}$ and $\mathbf{T}^*$, but stability is not analysed systematically.

In (Taber, 2008, 2009), the previous growth law is modified by adding evolution equations for the target stress:

$$\dot{\mathbf{G}}\mathbf{G}^{-1} = \mathbf{A}\left(\mathbf{T} - \mathbf{T}^*\right) \qquad \dot{\mathbf{T}}^*\left(\mathbf{T}^*\right)^{-1} = \mathbf{B}\left(\mathbf{T} - \mathbf{T}^*\right),$$

where $\mathbf{A}, \mathbf{B}$ are fourth-order tensors with constant entries. The systems analysed in these papers are practically the same as in (Ramasubramanian and Taber, 2008) and the conclusions are similar: For some parameter choices of $\mathbf{A}, \mathbf{B}, \mathbf{T}^*$ all taken at time $(t = 0)$ $\mathbf{T}$ and $\mathbf{T}^*$ converge to the same equilibrium value. In other cases, they converge to different equilibrium values, and in yet other cases the stresses diverge, reaching no equilibrium at all. One fundamental problem with this model is that the equilibrium values depend on the initial condition $\mathbf{T}^*\left(t = 0\right)$ which should not be the case in robust biological systems.

Based on the thermodynamic argument briefly discussed above, and discussed in more detail in Section 3.5, a growth law driven by Eshelby stress is proposed in (Ambrosi and Guana, 2007)

$$\dot{\mathbf{G}} = \mathbf{K}\left(\mathbf{E} - \mathbf{E}^*\right)\mathbf{G}, \tag{51}$$

where $\mathbf{E}$ and $\mathbf{E}^*$ are Eshelby stress and homeostatic Eshelby stress, respectively, and $\mathbf{K}$ is a matrix of constant coefficients. The proposition that Eshelby stress drives growth is supported by thermodynamical arguments ((Epstein and Maugin, 2000; Ambrosi and Guana, 2007; Ambrosi and Guillou, 2007)).

In (Ambrosi and Guana, 2007), the authors take as their starting point a growth law inspired by cardiovascular mechanics, in which $\mathbf{G}$ is diagonal (*i.e.* no shear) and involves only the circumferential components of Cauchy stress. For diagonal $\mathbf{G}$ and small deformations they show that (51) coincides with (50) up to a sign. By showing results of particular numerical simulations (but without a general stability result), the authors achieve convergence to the homeostatic stress in the case of displacement boundary conditions but obtain a divergent (ever-growing) in the case of prescribed load. Finally, they show that by adding passive layers (analysing a three rather than one-layered system, with inner and outer layers passive), convergence towards homeostasis is also possible when the load is prescribed.

3.5 Thermodynamic restrictions of growth laws

The standard procedure for for deriving restrictions to constitutive laws is known as the Coleman-Noll procedure (Coleman and Noll, 1963). The framework which has been built up around is known as rational thermodynamics. While it is very appealing for its axiomatic construction and

mathematical elegance, some of its assumptions are rather unorthodox and have been criticised as *e.g. 'adventurous'* (Maugin, 1999) and *'out of touch with physical reality'* (Lebon et al., 2008). However, for the treatment of thermoelastic solids, rational thermodynamics is quite elegant and produces equations which are consistent with elasticity and traditional (equilibrium) thermodynamics. For this reason, rational thermodynamics is widely used in the continuum mechanics community (Gurtin et al., 2010) and has found application to growing soft biological tissues.

Relevant ideas from rational thermodynamics The most important and useful objective of rational thermodynamics is to place restrictions on the constitutive relationships $\widehat{\Psi}$, $\widehat{\eta}$, $\widehat{\mathbf{T}}$ and $\widehat{\mathbf{q}}$ by means of the Clausius-Duhem inequality in the form (47). The standard procedure by which this is achieved is the Coleman-Noll procedure. Its objective is to restrict the constitutive relationships

$$\widehat{\Psi}\left(\mathbf{A}, \theta, \nabla\theta\right) \qquad \widehat{\eta}\left(\mathbf{A}, \theta, \nabla\theta\right) \qquad \widehat{\mathbf{T}}\left(\mathbf{A}, \theta, \nabla\theta\right) \qquad \widehat{\mathbf{q}}\left(\mathbf{A}, \theta, \nabla\theta\right). \quad (52)$$

It should be said that typically in solid mechanics literature unrelated to thermodynamics, the term 'constitutive relationship' relates to how strains are related to stresses, which is the terminology we use in Section 3.3. For hyperelastic materials, as described in Section 3.3, the constitutive relationship $\widehat{\mathbf{T}}\left(\mathbf{A}\right)$ can in fact be derived from a strain energy density $W(\mathbf{A})$. This is not assumed a priori in rational thermodynamics, but instead will be a result of the treatment of thermoelastic solids.[3] In the context of rational thermodynamics, constitutive relationships characterise a given material response. The Clausius-Duhem inequality, (47), with the constitutive assumptions incorporated and multiplied by J, is

$$J\rho\dot{\widehat{\Psi}} \leq J\widehat{\mathbf{T}} : \mathbf{F}\mathbf{F}^{-1} - J\rho\dot{\theta}\widehat{\eta} - \frac{J}{\theta}\widehat{\mathbf{q}} \cdot \nabla\theta + J\overline{\eta}. \quad (53)$$

It would be fair to ask at this point: If if in this context the Fourier heat flux $\widehat{\mathbf{q}}$ is considered a constitutive relationship, *i.e.* a material response, then why does this not apply to the heat source r in (43)? After all, r is a volumetric heat source (r stands for radiation) and $\widehat{\mathbf{q}}$ represents heat

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[3]Both the fact that $\widehat{\Psi}$, $\widehat{\eta}$, $\widehat{\mathbf{T}}$ and $\widehat{\mathbf{q}}$ have the same arguments and the fact that $\nabla\theta$ appears as a constitutive argument (in addition to the obvious thermo-elastic parameters θ, $\mathbf{A}$) are the results of Truesdell's *principle of equipresence*. In the words of G. A. Maugin, "This is simply a precautionary medasure to avoid missing any significant dependence or coupling" ((Maugin, 1999), p. 65). See also (Gurtin et al., 2010) p. 230 for a comment on equipresence.

entering through a volume boundary, see (43). Similarly, if $\widehat{\mathbf{T}}$ is a constitutive relationship, why not the body force $\widehat{\mathbf{b}}$ in (40)? The answer is that rather than prescribing $\mathbf{b}$ and r as constitutive relationships about which restrictions are to be inferred, they are *defined* in terms of the linear momentum balance (40) and energy balance (43), respectively. In other words, $\mathbf{b}$ and r are free parameters making sure that the momentum and energy balance are always satisfied, ruling them out of the restriction process of constitutive laws. As r and $\mathbf{b}$ are usually supplied in applications ($\mathbf{b}$ might be gravity, for instance), rational thermodynamics takes a somewhat *'perplexing attitude'*, in the words of (Lebon et al., 2008), with regard to these balance laws.

To complete the chain of ideas of the Coleman-Noll procedure, we point out that (53) is expected to hold for all admissible thermodynamic processes, which means that it must hold for arbitrary deformation gradients and temperature fields. Since the momentum and energy balance laws are ruled out by the argument in the previous paragraph, the fact that (53) must hold for all $\mathbf{A}$ and θ puts restrictions on the constitutive relationships (52).

Coleman-Noll procedure for morphoelasticity We now use the constitutive assumptions (52) to evaluate the Clausius-Duhem inequality (53). We analyse separately two important terms, $\dot{\widehat{\Psi}}$ and $J\widehat{\mathbf{T}} : \dot{\mathbf{F}}\mathbf{F}^{-1}$. By the chain rule,

$$\dot{\widehat{\Psi}}\left(\mathbf{A}, \theta, \nabla\theta\right) = \frac{\partial\widehat{\Psi}}{\partial\mathbf{A}} : \dot{\mathbf{A}} + \frac{\partial\widehat{\Psi}}{\partial\theta} : \dot{\theta} + \frac{\partial\widehat{\Psi}}{\partial\nabla\theta} \cdot \dot{\overline{\nabla\theta}}. \tag{54}$$

Evaluating $J\widehat{\mathbf{T}} : \dot{\mathbf{F}}\mathbf{F}^{-1}$ with $\mathbf{F} = \mathbf{A}\mathbf{G}$, we obtain

$$J\widehat{\mathbf{T}} : \dot{\mathbf{F}}\mathbf{F}^{-1} = J\widehat{\mathbf{T}}\mathbf{A}^{-T} : \dot{\mathbf{A}} + J\mathbf{A}^{T}\mathbf{T}\mathbf{A}^{-T} : \dot{\mathbf{G}}\mathbf{G}^{-1}. \tag{55}$$

We now regroup the terms and divide by J_G, taking into account $J_A\rho = \rho_r$ and $J = J_A J_G$ to obtain

$$\left(\rho_r\frac{\partial\widehat{\Psi}}{\partial\mathbf{A}} - J_A\widehat{\mathbf{T}}\mathbf{A}^{-T}\right) : \dot{\mathbf{A}} + \rho_r\left(\frac{\partial\widehat{\Psi}}{\partial\theta} + \eta\right)\dot{\theta} + \rho_r\frac{\partial\widehat{\Psi}}{\partial\nabla\theta} \cdot \dot{\overline{\nabla\theta}}$$

$$\leq \mathbf{A}^{T}\left(J_A\widehat{\mathbf{T}}\mathbf{A}^{-T}\right) : \dot{\mathbf{G}}\mathbf{G}^{-1} - \frac{J_A}{\theta}\widehat{\mathbf{q}} \cdot \nabla\theta + J_A\overline{\eta}. \tag{56}$$

We have made the assumption of a constant reference density (see comment after (36)), which without loss of generality allows us to define $\rho_r := 1$ *e.g.* by rescaling mass or volume.

As pointed out in the previous section, (56) is expected to hold for all deformation gradients and all temperature fields. But it is easy to construct a deformation gradient $\mathbf{A}$ and a temperature field θ which at a particular point and time $\mathbf{X}_0, t_0$ take values $\mathbf{A}(\mathbf{X}_0, t_0)$, $\dot{\mathbf{A}}(\mathbf{X}_0, t_0)$, $\theta(\mathbf{X}_0, t_0)$, $\dot{\theta}(\mathbf{X}_0, t_0)$, $\nabla\theta(\mathbf{X}_0, t_0)$, $\dot{\overline{\nabla\theta}}(\mathbf{X}_0, t_0)$ that are independent.[4]. For this reason, the coefficients of $\dot{\mathbf{A}}$, $\dot{\theta}$ and $\dot{\overline{\nabla\theta}}$ must vanish. Taking into account $\rho_r = 1$, it follows that

$$\mathbf{P}_r := J_A \widehat{\mathbf{T}} \mathbf{A}^{-T} = \frac{\partial \widehat{\Psi}}{\partial \mathbf{A}} \qquad \eta = -\frac{\partial \widehat{\Psi}}{\partial \theta} \qquad \frac{\partial \widehat{\Psi}}{\partial \nabla\theta} = 0. \tag{59}$$

This result demonstrates the elegance of rational thermodynamics. It shows that the first Piola-Kirchhoff $\mathbf{P}_r$ stress and the entropy are naturally derived from the thermodynamic potential $\widehat{\Psi}$ which is consistent with traditional nonlinear elasticity and thermodynamics. The Piola-Kirchhoff stress is given with respect to the stress-free configuration $\mathcal{B}_r$, as one would expect from traditional elasticity. It also shows that the free energy density is independent of the temperature gradient, suggesting (by equipresence, see footnote 3) that (52) should be updated to $\widehat{\Psi}(\mathbf{A}, \theta)$, $\widehat{\eta}(\mathbf{A}, \theta)$, $\widehat{\mathbf{T}}(\mathbf{A}, \theta)$, $\widehat{\mathbf{q}}(\mathbf{A}, \theta)$.

Taking into account (59), for (56) we obtain

$$0 \leq \mathbf{M} : \dot{\mathbf{G}}\mathbf{G}^{-1} + \frac{J_A}{\theta}\widehat{\mathbf{q}} \cdot \nabla\theta + J_A\overline{\eta}, \tag{60}$$

where we introduced the Mandel stress $\mathbf{M} := \mathbf{A}^T \mathbf{P}_r$.

Interpreting results of Coleman-Noll procedure   For simplicity, we assume that temperature is spatially homogeneous, such that the $\widehat{\mathbf{q}} \cdot \nabla\theta$ term drops out, which leaves

$$\mathbf{M}_r : \dot{\mathbf{G}}\mathbf{G}^{-1} + J_A\overline{\eta} \geq 0. \tag{61}$$

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[4]This is easy to show. We denote the values of $\mathbf{A}$, $\dot{\mathbf{A}}$, θ, $\dot{\theta}$, $\nabla\theta$, $\dot{\overline{\nabla\theta}}$ at the point $\mathbf{X}_0$, t_0 by underlined symbols $\underline{\mathbf{A}}$, $\underline{\dot{\mathbf{A}}}$, $\underline{\theta}$, $\underline{\dot{\theta}}$, $\underline{\nabla\theta}$, $\underline{\dot{\overline{\nabla\theta}}}$ We dropped the subscript m in θ for simplicity. The gradient is understood with respect to the reference variable $\mathbf{X}$, which we also dropped. Then

$$\mathbf{A}(\mathbf{X}, t) = \underline{\mathbf{A}} + (t - t_0)\underline{\dot{\mathbf{A}}} \quad \theta(\mathbf{X}, t) = \underline{\theta} + (t - t_0)\underline{\dot{\theta}} + \left[\underline{\nabla\theta} + (t - t_0)\underline{\dot{\overline{\nabla\theta}}}\right](\mathbf{X} - \mathbf{X}_0). \tag{57}$$

With this choice of $\mathbf{A}$ and θ, it simply follows

$$\mathbf{A}(\mathbf{X}_0, t_0) = \underline{\mathbf{A}} \quad \dot{\mathbf{A}}(\mathbf{X}_0, t_0) = \underline{\dot{\mathbf{A}}} \quad \theta(\mathbf{X}_0, t_0) = \underline{\theta} \quad \nabla\theta(\mathbf{X}_0, t_0) = \underline{\nabla\theta} \quad \dot{\overline{\nabla\theta}}(\mathbf{X}_0, t_0) = \underline{\dot{\overline{\nabla\theta}}}. \tag{58}$$

This shows that at $\mathbf{X}_0$, t_0, the quantities $\mathbf{A}$, $\dot{\mathbf{A}}$, θ, $\dot{\theta}$, $\nabla\theta$, $\dot{\overline{\nabla\theta}}$ can be chosen to have independent values $\underline{\mathbf{A}}$, $\underline{\dot{\mathbf{A}}}$, $\underline{\theta}$, $\underline{\dot{\theta}}$, $\underline{\nabla\theta}$, $\underline{\dot{\overline{\nabla\theta}}}$.

In the spirit of rational thermodynamics, restrictive statements about the growth law should only be the result of considering all possible deformations. We illustrate this idea with the simple growth law

$$\dot{\mathbf{G}} = \left(\widehat{\mathbf{T}} - \mathbf{T}^* \right) \mathbf{G}. \tag{62}$$

We assume that $\mathbf{G}$, $\dot{\mathbf{G}}$, $\widehat{\mathbf{T}}$ and $\mathbf{T}^*$ are diagonal and the material is incompressible ($J_A = 1$). In this case, the Mandel stress coincides with the Cauchy stress, $\mathbf{M}_r = \mathbf{T}$. Evaluating (61) yields

$$\widehat{\mathbf{T}} : \left(\widehat{\mathbf{T}} - \mathbf{T}^* \right) + \overline{\eta} = \left(\widehat{t}_1^2 + \widehat{t}_2^2 \right) + \left(\widehat{t}_1 t_1^* + \widehat{t}_2 t_2^* + \overline{\eta} \right) \geq 0. \tag{63}$$

The first bracketed term is positive or zero for any deformation and therefore it cannot contribute to a violation of the Clausius-Duhem inequality. In the second bracketed term, however, $\widehat{t}_1 t_1^* + \widehat{t}_2 t_2^*$ can potentially become negative at some point in space and time $\mathbf{X}_0, t_0$, and therefore requires an external source or sink of entropy to satisfy the Clausius-Duhem inequality. This could be provided by some biochemically driven self-organisation process. This suggests that a growth law of the form $\dot{\mathbf{G}} = \widehat{\mathbf{T}} \mathbf{G}$ is in principle microscopically achievable at every time and position in the tissue without further input or supporting mechanisms. However, no microscopic physical process could achieve the contribution $-\mathbf{T}^* \mathbf{G}$ without further supply of entropy that is information.

4 Conclusions

Growth processes are abundant in nature, yet the rules governing them are inherently complex. Moreover, growth occurs in different forms, and the varying types of growth may be fundamentally different both on a biological and a mathematical level. Theoretical and experimental analyses to understand growth processes on a mechanical level have been developed over a number of years. Of particular interest is the residual stress that can be induced in a body through growth: how and why does it arises? What role does it play in material and structure properties?

We have presented in this notes a summary of some of the key ideas and challenges underlying morphoelasticity. We illustrated the basic concept by considering one-dimensional growth where interesting and challenging questions arise. We then developed the full three-dimensional theory, with the question of how to think about a residually stressed body culminating in the fundamental idea of morphoelasticity, the decomposition of the deformation tensor into growth and elastic deformations. We then explore the thr

Many problems remain unsolved in morphoelasticity, and the theory itself is far from complete. One of the big future challenges in the field is in morpho-elastodynamics. In particular, we discussed a continuously growing body as satisfying a relation

$$\dot{\mathbf{G}} = \mathcal{G}(\mathbf{G}, \mathbf{A}, \mathbf{T}, \ldots, ; \mathbf{X}, t). \tag{64}$$

Finding appropriate biologically derived growth laws $\mathcal{G}$ presents a fundamental challenge for mechanics, applied mathematics, and biophysics.

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